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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/509,098	03/22/00	TSUCHIYA M	053466/0274

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EXAMINER	
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ART UNIT	PAPER NUMBER
1642	8

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Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary	Application No. 09/509,098	Applicant(s) TSUCHIYA, MASAYUKI	
	Examiner Larry R. Helms	Art Unit 1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *05 July 2001* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-13* is/are pending in the application.

4a) Of the above claim(s) *6-13* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-5* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) 3+4 .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

LGN

DETAILED ACTION

1. Applicant's election with traverse of Group I, claims 1-5 in Paper No. 7 is acknowledged. The traversal is on the ground(s) that "invention of Groups I and II exhibit the requisite special technical features" and "there is a technical relationship between inventions of Groups I and II regardless of alleged lack of novelty". This is not found persuasive. As stated in the restriction requirement, the "special technical feature" recited in claim 1 is not "special" as evidenced by Roguska et al and thus the Groups are not so linked as to form a single inventive concept under PCT Rule 13.1. In addition the response does not address the art of Roguska et al and in view of Roguska et al the technical feature recited in claim 1 is not "special".

The requirement is still deemed proper and is therefore made **FINAL**.

2. Claims 6-13 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected. Applicant timely traversed the restriction (election) requirement in Paper No. 7.

3. Claims 1-5 are under examination.

Specification

4. The disclosure is objected to because of the following informalities:

a. The first line of the specification should be updated to indicate that this application is a 371 of PCT/JP98/04469, filed 10/2/98.

Appropriate correction is required.

Claim Rejections - 35 USC § 112

5. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

6. Claims 1-5 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

a. Claims 1-5 are indefinite for reciting "natural humanized antibody" in claims 1-2 because the exact meaning of the phrase is not clear. Humanized antibodies are not found in "nature" they are produced by man, therefore it is not clear what the phrase means.

b. Claims 1-5 are indefinite for reciting "artificial amino acid residues" because the exact meaning of the phrase is not clear. Does the phrase mean unnatural amino acids, peptide mimetics, etc?

c. Claims 1-5 are indefinite for reciting incomplete method claims which do not clearly set forth method steps and does not include a resolution step which reads back on the preamble of the claimed method. Merely conducting a homology search and selecting and replacing different amino acids does result in a method of producing an antibody. The claims should conclude with a step producing the humanized antibody. Moreover, it is not clear whether the intended antibody binds any antigen.

d. Claims 1-5 are indefinite for reciting method claims which it is unclear if they are methods of designing an antibody, using a computer to design an antibody, or a method of producing an antibody molecule.

e. Claims 3-5 are indefinite for reciting "derived" in claims 3 and 5 because the exact meaning of the term is not clear. The term "derived" is not one which has a universally accepted meaning in the art nor is it one which has been adequately defined in the specification. The primary deficiency in the use of this phrase is the absence of a ascertainable meaning for said phrase. Since it is unclear how the "artificial amino acid residues" are to be derivatized to yield the class of derivatives referred to in the claims, there is no way for a person of skill in the art to ascribe a discrete and identifiable class of compounds to said phrase. Further, it is not clear if the "artificial amino acid residues are to be "derived" by attachment of a detectable marker, therapeutic molecule, some other molecule or altering the amino acid sequence, for examples. In addition, since the term "derived" does not appear to be clearly defined in the specification, and the term can encompass proteins with amino acid substitutions, insertions, or deletions, antibody fragments, chemically derivatized molecules, or even antibody mimetics. In absence of a single defined art recognized meaning for the phrase and lacking a definition of the term in the specification, one of skill in the art could not determine the metes and bounds of the claims.

f. Claim 2 is indefinite for reciting "replacing one or a plurality of different amino acid residues between the FR of the primary design antibody and the selected natural human FR" because the exact meaning of the phrase is not clear. It is unclear which

residues are to be replaced. Are the residues in the "natural human framework" to be replacing the amino acids in the "primary design antibody, or visa versa?

g. Claims 1-5 are indefinite for reciting "conducting a homology search for the FR of a primary design antibody" in claims 1-2 because the exact meaning of the phrase is not clear. What criteria is used for the search? What is being compared, homology of human FR to FR of "primary design antibody"? What homology, high homology or low homology?

h. Claims 1-2 and 5 are indefinite for reciting "primary design antibody" because the exact meaning of the phrase is not clear. Does the phrase mean an antibody that has been humanized, CDR grafted, a mouse antibody, or some other species of antibody?

i. Claims 1-5 are indefinite for reciting "selecting a natural human FR retaining the artificial amino acid residues contained in the FR of the primary design antibody" because the exact meaning of the phrase is not clear. Does the phrase mean selecting a FR that contains "artificial amino acid residues" or selecting a human FR that contains, for example, mouse FR sequences or selecting a human FR that is most homologous to the FR of the primary antibody?

Claim Rejections - 35 USC § 101

7. 35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

8. Claims 1-5 are rejected under 35 U.S.C. 101 because the claimed invention is directed to non-statutory subject matter. This determination was made based MPEP2106. This was used to determine whether a claimed invention complies with 35 U.S.C. 101. The interpretation is based on the breath of 35 U.S.C. 101. This analysis initiates by classifying the claimed invention based on three initial questions. The first question is whether the claimed invention is "functional descriptive material such as data structure per se or computer program per se". The second is whether the claimed invention is "non-functional descriptive material (e.g., music, literary works, mere data) per se or on computer readable medium". The third is whether the claimed invention is "a natural phenomenon (e.g., energy or magnetism)". The answer to all of these questions is NO. This answer leads to further classification asking if the claimed invention is "A series of steps to be performed on a computer?". The answer to this question is YES.

The next step is based on two questions to evaluate the process to determine if it "performs independent physical acts (post-computer process activity)" or "Manipulates data representing physical objects or activities to achieve a practical application (pre-computer process activity)". The answer to these questions is NO. This results in a final evaluation or question of does the claimed invention "Merely manipulates abstract idea or solves a purely mathematical problem without any limitation to a practical application"? This answer for the claimed invention is YES.

The analysis based on the MPEP indicates non statutory subject matter. The claims lacks physical steps being drawn only to mental steps which are not considered

statutory subject matter. The only active steps in the independent claims are drawn to "conducting a homology search" and "replacing one or a plurality of different amino acid residues" which can be performed on a computer or on paper. The dependent claims do not correct this deficiency by providing a physical step. The lack of a pre or post solution activity renders the claims non statutory.

Claim Rejections - 35 USC § 102

9. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

10. Claims 1-3 and 5 are rejected under 35 U.S.C. 102(b) as being anticipated by Sato et al (Molecular Immunology 31:371-381, 1994, IDS #4).

The claims recite a method for preparing a natural humanized antibody comprising conducting a homology search for the FR and selecting a human Fr having homology to the primary design antibody and replacing one or a plurality of different amino acids between the FR of the primary antibody and the human FR, wherein the CDRs are from a first species and the FR is from a second species, wherein the artificial amino acid residues are derived from the Fr of a non-human antibody.

Sato et al teach a method for humanization comprising CDR grafting by a homology search between the mouse antibody and human FR regions and selecting the most homologous and then comparing the resulting designed antibody to the

consensus sequences for a subgroup to identify any highly irregular sequences (see entire document, especially page 380, right column).

11. Claims 1-3 and 5 are rejected under 35 U.S.C. 102(b) as being anticipated by Co et al (Proc. Natl. Acad. Sci. USA 88:2869-2873, 1991, IDS #4).

The claims have been described supra.

Co et al teach a method for humanization comprising CDR grafting by a homology search between the mouse antibody and human FR regions and selecting the most homologous and then replacing mouse residues with human residues because of the mouse residues were rare in the human antibodies and this would eliminate the unusual amino acids in the FR which may further reduce immunogenicity (see entire document, especially page 2871, right column).

12. Claims 1-3 and 5 are rejected under 35 U.S.C. 102(b) as being anticipated by Roguska et al (Protein Engineering 9:895-904, 10/96, IDS #3).

The claims have been described supra.

Roguska et al teach a method of humanization comprising CDR grafting by a homology search between the mouse antibody and human FR regions and selecting the most homologous and then replacing residues in the antibody with those found in the human FR (see page 898, left column, GN901v1.1).

Claim Rejections - 35 USC § 103

13. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

14. Claims 1-5 are rejected under 35 U.S.C. 103(a) as being unpatentable over Sato et al (Molecular Immunology 31:371-381, 1994, IDS #4) and Co et al (PNAS 88:2869-2873, 1991, IDS #4) and Roguska et al (Protein Engineering 9:895-904, 1996, IDS #3) as applied to claims 1-3 and 5 above, and further in view of Queen et al (PNAS 86:10029-10033, 1989, IDS #4).

Claims 1-3 and 5 have been described supra.

Claim 4 recites wherein the first animal species is rat and the second animal species is human.

Sato et al, Co et al , and Roguska et al have been described supra. Sato et al, Co et al , and Roguska et al do not teach a rat species. This deficiency is made up for in the teachings of Queen et al.

Queen et al teach a method of humaization comprising CDR grafting and homology searching and replacing FR residues and the species mouse and rat (see entire document, especially page 10029, right column, first full paragraph).

It would have been prima facie obvious to one of ordinary skill in the art at the time the claimed invention was made to have used the a rat antibody for humanization as taught by Queen et al in the methods of Sato et al, Co et al , and Roguska et al. One of ordinary skill in the art would have been motivated to and had a reasonable expectation of success to have used the a rat antibody for humanization as taught by Queen et al in the methods of Sato et al, Co et al , and Roguska et al because Queen et al teach that one can use either a mouse or a rat antibody for humanization. Moreover, one of ordinary skill in the art would have been motivated to and had a reasonable expectation of success to have used the a rat antibody for humanization as taught by Queen et al in the methods of Sato et al, Co et al , and Roguska et al because it was routine in the art at the time the claimed invention was made to use mouse as well as rat and other non-human a species as the antibody to humanize.

Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references.

Conclusion

15. No claim is allowed.

16. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Larry R. Helms, Ph.D, whose telephone number is (703) 306-5879. The examiner can normally be reached on Monday through Friday from 7:00 am to 4:30 pm, with alternate Fridays off. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anthony Caputa, can be reached on (703) 308-3995. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

17. Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center telephone number is (703) 305-7401.

Respectfully,

Larry R. Helms Ph.D.

703-306-5879

Sheela J. Huff
SHEELA HUFF
PRIMARY EXAMINER